

Impaired visual processing of contralesional stimuli in neglect patients: a visual-evoked potential study

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Transient visual-evoked potentials (VEPs) were recorded in 11 patients with right brain damage and spatial neglect. High-resolution EEG was recorded using focal stimuli located in the four visual quadrants. VEPs to left stimuli, i.e. located in the neglected side, were compared to VEPs to right stimuli. Results showed that bottom-up processing of a visual stimulus located in the neglected hemifield was intact up to ~130 ms from stimulus onset. Hemispheric differences were not significant for either CI or PI components representing the activity of striate and extrastriate areas, respectively. In contrast, visual processing in more dorsal areas adjacent to the superior parietal lobe was changed from normal. We failed to record the N1a component for left visual field stimuli expected in the 130–160 ms time range. Furthermore, the N1p (140–180 ms) and P2 (180–220) components were delayed and/or reduced in amplitude for stimuli located on the neglected side. The source of the N1a was previously localized in the intraparietal sulcus in the dorsal occipital cortex; N1p may represent a reactivation of area V3A and P2 reactivation of occipital visual areas including V1 due to top-down feedbacks. Six patients with left brain damage (LBD) and no neglect and 21 healthy subjects were also tested in the same experimental conditions used for patients with neglect. In LBD patients, all components evoked by contralesional stimuli were comparable to ipsilesional components. Overall, data allow localizing in time and space the processing deficit specific for patients with neglect. The first takes place around 130 ms in the bottom-up processing at the level of the anatomically intact dorsal parietal areas; the second is located at the level of the reactivation of the striate and extrastriate areas via feedback connections from higher visual areas. The two functional impairments were limited to left-field stimuli.

Keywords: neglect; visual cortex; pattern-onset VEP; visual quadrants; neuropsychology; attention deficit

Abbreviations: ERP = event-related potentials; LVF = left visual field; RVF = right visual field

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Introduction

Unilateral spatial neglect (hereafter called neglect) may follow unilateral brain damage; the disorder is relatively common and persistent after cerebral vascular damage to the right hemisphere (while it is rare and transitory after left-brain damage) (e.g. Bisiach and Vallar, 2000). The lesions are typically large and diffuse, involving the right inferior parietal cortex, the ventral frontal cortex and the superior temporal cortex (e.g. Committeri *et al.*, 2007). Neglect patients fail to respond, orient to or report stimuli

located in the left contralesional space (e.g. Bisiach and Vallar, 2000).

The observation that neglect may be detected in different sensory modalities, its presence in cognitive tasks, such as imagery, and the notion that primary sensory areas are generally spared support an interpretation of the disorder in terms of a high-order deficit (Heilman and Valenstein, 1979) rather than a sensory-perceptual one (Denny-Brown *et al.*, 1952). This largely accepted view leads to the implicit corollary assumption that sensory processing of

contralesional stimuli is intact. Early event-related potentials (ERPs) studies confirmed this idea, reporting normal cortical activity evoked by stimuli located on the neglected side (Lhermitte *et al.*, 1985; Vallar *et al.*, 1991; Viggiano *et al.*, 1995). In contrast, some electrophysiological data and recent functional magnetic resonance (fMRI) data support the view that changes in contralesional stimulus processing are present.

In various studies investigating the visual domain, we found that contralesional-evoked activity was different from ipsilesional-evoked activity. Steady-state visual-evoked potential (SSVEP) apparent latencies to contralesional stimuli were systematically longer (10–30 ms) than ipsilesional ones (Spinelli *et al.*, 1994; Spinelli and Di Russo, 1996; Pitzalis *et al.*, 1997) (See also supplementary Tables I and II). Verleger and co-workers noted that the N1 component evoked by left visual field (LVF) stimuli was reduced at the right recording site (Verleger *et al.*, 1996). With fMRI, Corbetta and coworkers showed that, in acute neglect patients, the anatomically intact right striate cortex was less activated by visual stimulation than the left striate cortex and that the response to contralesional stimuli in the right cortex was smaller than the ipsilesional response (Corbetta *et al.*, 2005).

In the auditory domain, Deouell and co-workers (e.g. Deouell *et al.*, 2000) showed that the N1 component (peak between 70 and 130 ms) evoked by left- and right-sided stimuli was larger over the intact hemisphere in neglect patients and was larger over the hemisphere contralateral to the side of stimulation in healthy subjects. Further, differences between contralesional- and ipsilesional-evoked activity were observed in the mismatch negativity (MMN, peaking between 100 and 250 ms), associated with a pre-attentive mechanism.

Somewhat similar results were obtained in extinction patients. The P1 and N1 components were absent or reduced for the extinguished visual stimulus with respect to the perceived stimulus (Marzi *et al.*, 2000; Driver *et al.*, 2001). Marzi and co-workers also investigated extinction patients using unilateral stimulation. In this condition, the P1 component was found to be highly variable across patients; the N1 component (140–200 ms) evoked in the right hemisphere by LVF stimulation (the extinction side) was smaller than the response evoked in the left hemisphere by right visual field (RVF) stimulation (Marzi *et al.*, 2001; similar results in Driver *et al.*, 2001). Impairment of callosal transfer was reported by Vuilleumier *et al.*, 2001. fMRI studies found stronger activation for consciously detected vs. extinguished stimuli in visual cortices including the primary visual area (V1) in the right hemisphere (Driver *et al.*, 2001) or not including V1 (Rees *et al.*, 2000; Vuilleumier *et al.*, 2001).

Although some contrasts are present in the data reported above (differences among studies are not surprising considering the variability of patients and techniques (ERP vs. fMRI or, within ERPs studies, different stimuli

and different recording characteristics), we may summarize saying that (i) early sensory cortices are activated by stimuli that escape awareness (see also Driver *et al.*, 2001) and (ii) differential activation between perceived vs. neglected/extinguished stimuli are clearly documented. Thus, contralesional stimulus processing in neglect (and extinction) is different from normal processing (see Marzi *et al.*, 2001 for a similar conclusion). What remains to be defined is the level (or levels) of processing at which such changes take place. The present work is devoted to this aim, limited to the visual domain.

In our previous studies, based on the hypothesis that SSVEPs mostly reflect V1 activity and considering that the occipital cortex was intact in most neglect patients studied, we speculated that the observed changes should reflect functional changes. These changes might be due to an abnormal top-down feedback by higher cortical areas to visual cortices, including V1 (Spinelli *et al.*, 1994). This speculation is now reinforced by a study in normal subjects showing that the main generators of SSVEPs are V1 and the middle temporal cortex (MT) (Di Russo *et al.*, 2007). An alternative hypothesis, proposed by Marzi and co-workers (2001) in a discussion of extinction patients' data, is that abnormal processing of contralesional stimuli occurs beyond V1 at a level corresponding, in terms of information processing, to the focusing of spatial attention.

In the present study, we investigated the neural level (or levels) at which changes from normal can be detected in neglect by evaluating the functional integrity of (i) the processing stages representing bottom-up visual activity and (ii) the reactivation of visual cortices representing top-down feedback modulation.

To pursue this aim, we took advantage of the high temporal resolution of the transient VEPs and the spatial resolution provided by a dense recording array. We measured the integrity of the different processing stages by examining various VEP components. The methodological basis for such an approach was provided by our previous experience with healthy subjects using VEP and fMRI in conjunction (Di Russo *et al.*, 2002b). This allowed for a very accurate source localization of different VEP components. Here, we applied in patients with neglect the same stimulus paradigm and recording set-up to study the following five VEPs components.

The first investigated component was the C1 (also called N75) which reflects the activity of the primary visual cortex V1 about 60–100 ms after stimulus onset. The second component was the P1 (also called P100). The P1 reflects the conjoined activity of the dorsal visual areas V3A and the ventral V4 in the 85–130 ms range.

The third investigated component was the N1a. In the past, the N1 component present in the 130–180 ms time window was considered a single component; however previous studies (Clark *et al.*, 1995; Clark and Hillyard, 1996; Martinez *et al.*, 2001; Di Russo *et al.*, 2002b) showed that N1 is actually a complex including two major

sub-components, the anterior N1 (130–160 ms; here referred to as N1a) and the posterior N1 (140–180 ms; here referred to as N1p). A study combining ERP and fMRI data, showed that the N1a (peaking on central sites) seems to reflect the activity within the intraparietal sulcus (IPS) in the dorsal parieto occipital cortex (Di Russo *et al.*, 2002b); this was confirmed by further studies in different laboratories (Di Russo *et al.*, 2003, 2005). According to this view, N1a reflects bottom-up stimulus processing at a level (dorsal IPS areas) dealing with spatial attention and visuo-motor control (eye and hand movements; e.g. Astafiev *et al.*, 2003).

The fourth and fifth investigated components were the N1p and P2. Both may be considered reactivation of the occipital lobes. The notion of reactivation of visual cortices is relatively new, and few investigations in humans try to define specific ERPs components marking this process. It is widely known that reciprocal interconnections between most areas of the visual cortex are rich (e.g. Felleman and van Essen, 1991) and that there are at least as many fibres feeding back into the primary cortex area as fibres feeding forward. The role of the backward connections is in the modulation of the activity of lower areas, possibly to control information analysis at early levels (e.g. Tononi *et al.*, 1992); however only recent data on single cells have directly supported this view (e.g. Sillito *et al.*, 2006). In humans, the highly sensitive chronometric information of ERPs plus source analysis studies associated with fMRI are, at present, the best method available to investigate activation and re-activation of visual areas. The occipital region is activated first at 60–100 ms from stimulus onset (C1 and P1 components), then again 80 ms later (N1p), and again (P2 component) with a temporal delay of 120 ms from C1 onset. It has been proposed (e.g. Di Russo *et al.*, 2003) that N1p reflects a reactivation of the extrastriate visual areas V3A, while the P2 (or P200) component (peak latency around 180–220 ms) involves reactivation of occipital areas including V1. Thus, N1p and P2 may be considered feedbacks from higher areas on extrastriate and striate areas.

Data collected in several laboratories has provided converging evidence to the view of reverberating activity as top-down feedback on early visual areas in attentional tasks 140–220 ms after the stimulus onset. Martinez *et al.* (2001) and Noesselt *et al.* (2002) combined ERP and fMRI data; Barnikol *et al.* (2006) and Murray *et al.* (2002) combined magneto-encephalogram (MEG) and VEP/fMRI data to show the effect of recurrent activation mechanisms including V1 and extrastriate areas and corticofugal feedback loops. Olson and colleagues (2001) recorded intracranial ERPs in humans and found reactivation feedbacks in areas V1 and V2 beginning 200 ms after the stimulus onset. Overall, in the present study, on the basis of evidence reported above, we assume that both N1p and P2 are feedback from higher areas on extrastriate and striate areas.

In the present study, we tested the efficiency of bottom-up neural processing of contralesional stimuli from V1 to IPS in the dorsal parieto-occipital cortex. Considering that these regions are usually spared in neglect patients, we suggest that a sensory function may be abnormal even if the sensory area is anatomically intact. Similarly, visuo-motor behaviour may be impaired, as in neglect, even if the region representing a plausible substrate for neglect, i.e. the dorsal parietal cortex, is anatomically intact [see the model of Corbetta *et al.* (2005)]. Indeed the ERPs are a very sensitive method to test the *functional integrity* of cortical areas.

One specific goal of the study was to link the data of our previous studies using SSVEP in neglect with the present data of transient-VEPs. In particular, we aimed to test the hypothesis of a change from normal in the top-down feedback to visual cortices. Thus we measured modifications to N1p and P2 components, which we consider expressions of top-down feedback.

Material and Methods

Subjects and plan of the study

We studied 11 patients with unilateral lesions of the right hemisphere and visuo-spatial neglect (Table 1, N1–11). In this group, as well as in the other groups, we compared ERPs to left and right visual field stimuli; thus, each patient (subject) had himself/herself as a control. As an additional control, we studied six patients with unilateral lesions of the left hemisphere and without neglect (Table 1, L1–6). Patients were selected according to demographic and clinical characteristics. All patients had vascular pathologies. Lesions, assessed with MRI scans, were large and heterogeneous, generally involving many cortical and sub-cortical areas. No occipital lesions were reported. The presence of spatial neglect was assessed using a standard neuropsychological battery of tests that included two cancellation tasks (Line and Letter Cancellation tests), the Wundt–Jastrow Area Illusion test and the Sentence Reading test. Patients who failed on at least two out of the four tests were classified as neglect patients (Pizzamiglio *et al.*, 1989). All left brain damage (LBD) patients scored within the normal range on the four tests. All patients had intact visual fields based on standard kinetic Goldmann perimetry and were chosen on the basis of their ability to keep the fixation for at least 30 s. The two groups of patients did not differ for sex ($\chi^2 = 0.69$; ns), age ($t_{(15)} = 1.04$ ns), time from lesion ($t_{(15)} = 1.92$ ns) or schooling ($t_{(15)} = 0.23$ ns). Additional statistical comparisons were run between the two groups of patients in order to evaluate some specific questions (see additional analyses in the results section). To link present data to the previous high-resolution source localization study combining fMRI and VEPs (Di Russo *et al.*, 2002b) conducted in a different laboratory, 21 healthy subjects were also tested. The healthy group was much younger than the patients group and was not used for statistical comparison with the patients groups. Mean age of healthy subjects (nine females) was 30.4 years. Informed consent was obtained from each participant; all procedures were approved by the local ethics committee. All participants were right-handed and had normal or corrected-to-normal visual acuity.

Table 1 Demographic and clinical data of neglect (N) and LBD (L) patients

Patient	Age	TFO	Sex	Lesion aetiology	Lesion type	Lesion site	Line cancell.	Letter cancell.	Wundt–Jastrow	Sentence Reading
N1	55	105	M	I	C	R-FTP	+	+	+	+
N2	78	162	M	I	C	R-FP	–	+	+	+
N3	48	77	F	H	C	R-P	–	+	+	–
N4	71	125	F	I	CSC	R-FTP	+	+	+	+
N5	77	82	F	I	CSC	R-F	–	+	+	–
N6	51	445	M	I	CSC	R-F	–	+	+	–
N7	60	99	M	I	C	R-TP	–	+	+	+
N8	50	271	F	I	C	R-FTP	–	+	+	–
N9	71	293	M	I	CSC	R-FP	–	+	+	+
N10	71	130	M	I	CSC	R-FTP	+	+	–	+
N11	69	227	F	I	CSC	R-FTP	–	+	+	–
Mean	63.7	183								
L1	55	485	M	I	CSC	L-F	–	–	–	–
L2	65	68	M	I	C	L-P	–	–	–	–
L3	56	164	F	I	CSC	L-TP	–	–	–	–
L4	71	52	M	I	C	L-TP	–	–	–	–
L5	67	467	M	H	C	L-FP	–	–	–	–
L6	50	32	F	I	CSC	L-FTP	–	–	–	–
Mean	60.7	211								

TFO = time from onset (days). Lesions aetiology (MRI data): H = haemorrhagic, I = ischaemic. Lesions type: C = cortical, SC = sub-cortical, CSC = cortical-subcortical. Lesion site: L = left, R = right, F = frontal, T = temporal, P = parietal. Neglect tests: + identifies pathological performances according to standard normative values (Pizzamiglio *et al.*, 1989).

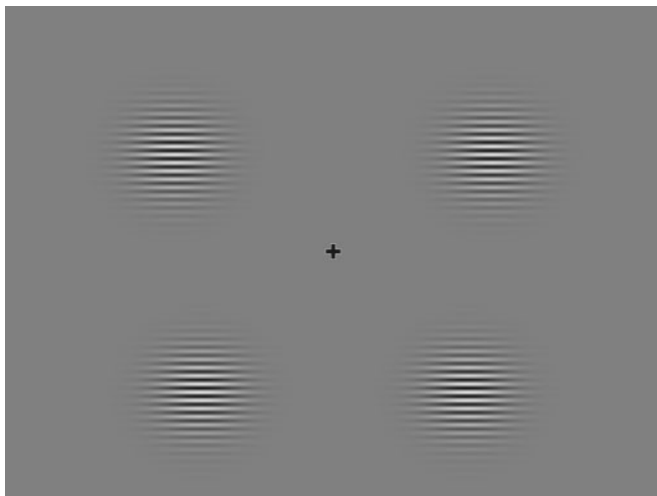


Fig. 1 Stimuli used in the experiment. Circular Gabor gratings were flashed at one of the four locations in random order. The size, spatial frequency and location of stimuli were selected in order to better differentiate the contribution of different brain areas.

Stimuli

The stimuli consisted of small circular Gabor gratings, which were modulated sinusoidally in black and white and horizontally oriented (Fig. 1); each stimulus had a diameter of 2 of visual angle and a spatial frequency modulation of 3 cycles per degree. Stimuli were flashed for a 66 ms duration against a gray background (22 cd/m^2) that was equiluminant with the mean luminance of the grating pattern, which was modulated at a contrast of 32%. Stimuli were presented binocularly in randomized

sequences in the four quadrants of the left visual field (LVF) and right visual field (RVF) at a fast rate (SOAs varying between 350 and 650 ms). Stimulus positions were centered along an arc that was equidistant (4°) from a central fixation point. For more details, see the supplementary methods.

Procedure

Participants were comfortably seated in a dimly lit sound-attenuated and electrically shielded room while stimuli were presented on a video monitor at a viewing distance of 114 cm. Subjects were trained to maintain stable fixation on a central cross (0.2°) throughout stimulus presentation. Each run lasted 120 s followed by a 30 s rest period, with longer breaks interspersed. A total of 18 runs or more were carried out in order to deliver at least 800 stimuli to each quadrant. The subjects were given feedback on their ability to maintain fixation, and EEG recording was paused each time the subject lost fixation.

Electrophysiological recording and data analysis

The EEG was recorded using a BrainVision system from 64 electrodes placed according to the 10–10 system montage (Di Russo *et al.*, 2002b). All scalp channels were referenced to the left mastoid (M1). Horizontal eye movements were monitored with a bipolar recording from electrodes at the left and right outer canthi. Blinks and vertical eye movements were recorded with an electrode below the left eye, which was referenced to site Fp1. The EEG from each electrode site was digitized at 250 Hz with an amplifier bandpass of 0.01–60 Hz, including a 50 Hz notch filter, and was stored for off-line averaging. Computerized artifact rejection was performed prior to signal averaging in order to discard epochs in which deviations in eye position, blinks or amplifier blocking occurred. All epochs (from -100 to 500 ms

after the stimulus onset) in which EOG amplitudes were greater than $\pm 80 \mu\text{V}$ and EEG amplitudes were greater than $\pm 60 \mu\text{V}$ were excluded from further analysis. On average, 9.5%, 19% and 20% of the trials were rejected for violating these artifact criteria in the healthy subject, LBD and Neglect group, respectively. VEPs were averaged separately for stimuli in each quadrant in epochs that began 100 ms prior to the stimulus onset and lasted for 1100 ms. The amplitudes of the different VEP components were measured as peak values within specified windows with respect to the 100 ms pre-stimulus baseline. Three-dimensional topographical maps of scalp voltage over time were obtained for the VEPs to stimuli in each of the four quadrants using the BESA 2000 V5.1.4 system.

Separate analyses of variance (ANOVAs) were used to evaluate hemispheric differences within each group on the different VEP components. The ANOVA factor was Hemifield (left vs. right). Separate ANOVAs were conducted on amplitudes and latencies for each VEP component of interest (i.e. C1, P1, N1a, N1p and P2). Component amplitudes were measured as peak voltage deflections within five specified time intervals (70–90, 90–120, 130–160, 140–200 and 200–280 ms) with respect to a 100 ms pre-stimulus baseline. These intervals were the same for all groups and were based on previous studies which used the same VEP paradigm (Di Russo *et al.*, 2002b, 2003). The analyses of the VEP components were based on the grand average of each group and were carried out at the electrode sites where the components were maximal in amplitude, separately for VEPs to upper and lower field stimuli. A further analysis was conducted in the patients groups using the electrodes selected in the grand average of the healthy subject group. The Greenhouse-Geisser correction was applied to the results. The significance level was set at $P < 0.05$.

Results

VEP waveforms and topography

Neglect patients

The spatio-temporal structure of the VEPs to stimuli in each of the four quadrants is shown in Fig. 2. The major components' amplitudes, latencies and topographic properties are reported in Table 2. In the same table are also reported the statistical comparisons between responses to left and right stimuli for this group of patients.

The earliest component (C1) had an average onset latency of about 55 ms and a peak latency of 80–84 ms. For upper field stimuli, the C1 was most prominent at ipsilateral occipito-parietal sites, close to the midline; for lower field stimuli, the C1 was largest at contralateral occipito-parietal sites, close to the midline. In all subjects, the C1 varied systematically in polarity as a function of stimulus position, i.e. it was negative for stimuli in the upper fields and positive for stimuli in the lower fields. Hemispheric differences were not significant (all P -values > 0.5).

Overlapping in time with the C1, the P1 component was elicited at contralateral occipito-temporal sites. This component had an average onset latency of 70 ms and peak latency of 110 ms for the upper fields (95 ms for the lower fields). These latency differences are most likely attributable

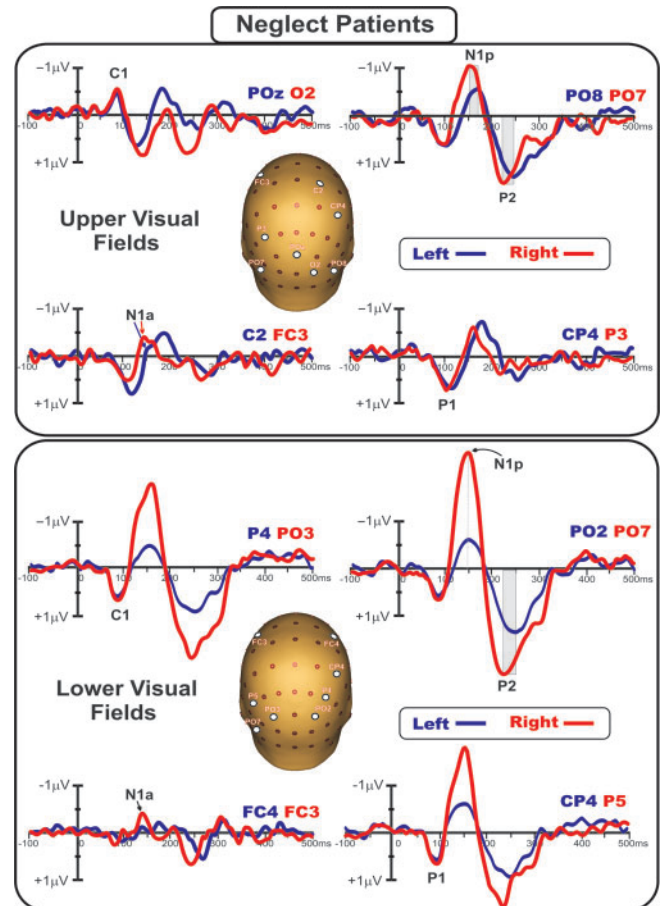


Fig. 2 Neglect patients. Grand-averaged VEPs to stimuli located in the left (blue lines) and right (red lines) visual fields. Electrode locations correspond to the peak activity of labeled VEP components. N1a = anterior N1, N1p = posterior N1. The negative activity present for the upper left quadrant around 180 ms on C2 electrode is part of the later N1p component peaking on posterior sites, as shown in Fig. 3. Waveforms are derived by more than 7200 trials per quadrant.

to overlap with the polarity inverting C1 (e.g. Di Russo *et al.*, 2002b). The P1 did not change in polarity and varied little in amplitude for stimuli in the upper vs. lower hemifields. Hemispheric differences were not significant (all P -values > 0.5).

While hemispheric differences were not significant for the earlier components, these were evident for components with latencies longer than 130 ms. Responses to contralateral stimuli were clearly defective.

In the interval between 130 and 180 ms, several negative waves were elicited concurrently at different scalp locations. This complex of spatially and temporally overlapping waves is often referred to collectively as the N1 component; however, recent studies have detected two different sub-components: N1a and N1p (e.g. Martinez *et al.* 2001). The two sub-components were well detectable in healthy subjects and LBD patients (see below) and quite well detectable in the ipsilesional responses of patients with neglect. In contrast, one of the two sub-components (N1a)

Table 2 VEP components identified in neglect patients

VEP component	Stimulus position	Peak electrode	Peak latency	P-value	Peak amplitude	P-value
C1 (70–90 ms)	Upper left	POz	82	ns	−0.49	ns
	Upper right	O2	82		−0.53	
	Lower Left	P4	82	ns	0.71	ns
	Lower Right	PO3	84		0.84	
P1 (90–120 ms)	Upper left	CP4	110	ns	0.70	ns
	Upper right	P3	100		0.75	
	Lower Left	CP4	95	ns	0.68	ns
	Lower Right	P5	95		0.73	
N1a (130–160 ms)	Upper left	C2	145	ns	0.05	<0.05
	Upper right	FC3	140		0.42	
	Lower Left	FC4	135	ns	0.07	<0.05
	Lower Right	FC3	135		0.35	
N1p (140–200 ms)	Upper left	PO8	168	<0.01	−0.63	<0.05
	Upper right	PO7	150		−1.03	
	Lower Left	PO2	147	ns	−0.64	<0.01
	Lower Right	PO7	144		−2.48	
P2 (200–280 ms)	Upper left	PO8	245	<0.05	1.28	ns
	Upper right	PO7	220		1.46	
	Lower Left	PO2	244	<0.05	1.12	<0.05
	Lower Right	PO7	224		2.10	

Latencies (ms) and amplitudes (μV) are measured on the corresponding peak electrode within the indicated interval. P-values indicated the statistical comparison between left and right visual fields. ns = not-significant.

was absent for contralesional stimuli in the patients with neglect.

A small N1a component was present for the RVF; it was prominent at contralateral frontal-central sites and peaked at 135–140 ms. The same component was not detectable for LVF. Obviously, statistical hemispheric comparisons, made on the peak value in the specific time window, were significant for both upper and lower quadrants. Moreover, to statistically test the absence of the N1a component for LVF stimuli, we compared responses' amplitudes (0.05 and 0.07 μV for upper and lower fields, respectively) to the 100 ms pre-stimulus baseline. The differences were not significant ($t_{10} < 1$ ns).

The N1p component was distributed over contralateral parieto-occipital sites. The N1p component evoked by the contralesional stimulus, resulted significantly delayed ($P < 0.01$) and reduced in amplitude ($P < 0.01$) for the upper left stimulus compared to the upper right one. For the lower fields, the N1p to left stimuli resulted reduced in amplitude ($P < 0.01$) but not significantly changed in latency with respect to right stimuli.

The fifth investigated component was the positive wave P2, distributed over contralateral parieto-occipital sites. The P2 component evoked by the contralesional stimulus was significantly delayed ($P < 0.01$) but not reduced in amplitude (even though a tendency was present) for the upper portion of the visual field. For the lower fields, the P2 was both delayed ($P < 0.01$) and reduced in amplitude ($P < 0.01$) with respect to the ipsilesional component.

Voltage topographies

Figure 3 shows the voltage topographies of the components found in the neglect patients. The C1 component was negative and maximal in amplitude between the occipito-parietal midline for the upper left stimulus and ipsilateral for the upper right stimulus. For the lower field stimuli, C1 amplitude was positive and maximal at contralateral occipito-parietal sites. The P1 was largest over contralateral parietal sites; its focus was located more superiorly for stimuli in the lower fields.

The N1a, detectable for right stimuli only, was largest on contralateral fronto-central sites. For the upper LVF, some negative activity was present around 180 ms on central electrodes (C2 electrode in the upper panel of Fig. 2). To exclude the likelihood of a delayed N1a, the scalp topography in the upper panel of Fig. 3 shows a clear posterior distribution at around 170 ms, which is more likely ascribable to an anterior spreading of a later N1p component peaking on posterior sites. At 180 ms the topography (not shown) was very similar to that shown in Fig. 3. The N1p was largest over the contralateral temporal-occipital sites. Finally, the P2 was distributed over the contralateral occipito-temporal site for the upper fields and at the contralateral occipital sites close to the midline for the lower fields.

Healthy subjects and LBD patients

The spatio-temporal structure of the VEPs to stimuli in each of the four quadrants is shown in Figs 4 and 5 for

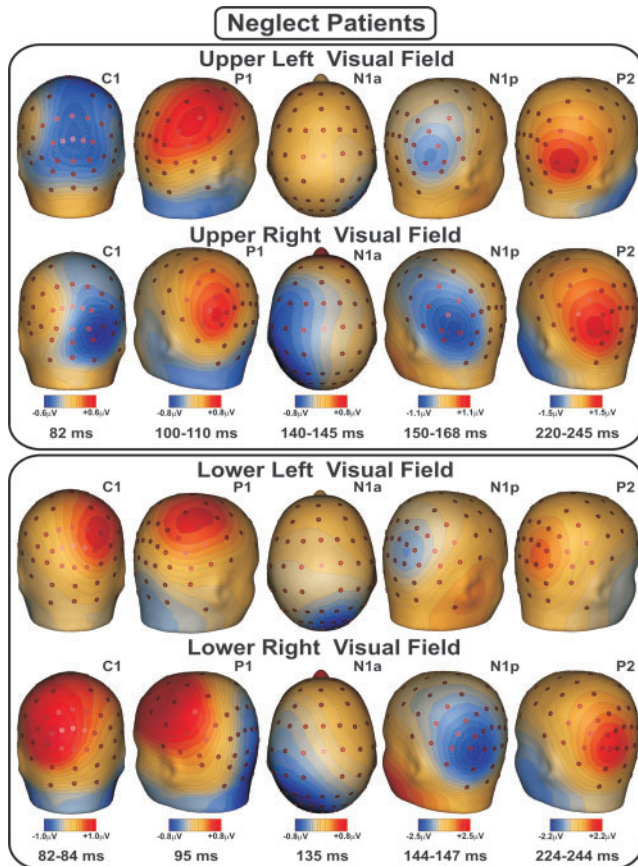


Fig. 3 Neglect patients. Spline-interpolated 3D voltage maps in the neglect patients' group of VEP components elicited by stimuli in each quadrant. Latencies of maps are indicated below each panel. Note that for LVF stimuli in both upper and lower quadrants the brain activity at the latency corresponding to the expected latency for the N1a component was not symmetrical to the activity recorded for the RVF stimuli.

healthy subjects and LBD patients, respectively. The major components' amplitudes, latencies and topographic properties are reported in Tables 3 and 4 (for voltage maps see Figs 6 and 7) for healthy subjects and LBD patients, respectively. In the same tables are also reported the statistical comparison between responses to left and right stimuli within each group. The main result is that, for both groups and for all five components investigated, the latency and the amplitude of responses to right and left stimuli were comparable (all *P*-values were non-significant).

Similar to neglect patients, the earliest component (C1) in both healthy subjects and LBD patients had an average onset latency of about 55 ms and a peak latency of 80–84 ms. Distribution and polarity of the C1 component for upper and lower field stimuli was similar to that described above for patients with neglect. The only difference between the data on healthy subjects and patients (both LBD and neglect) was the amplitude of the C1 component, which was larger in the healthy group.

The P1 component had an average onset latency of 72–80 ms and a peak latency of 105 ms for the upper fields

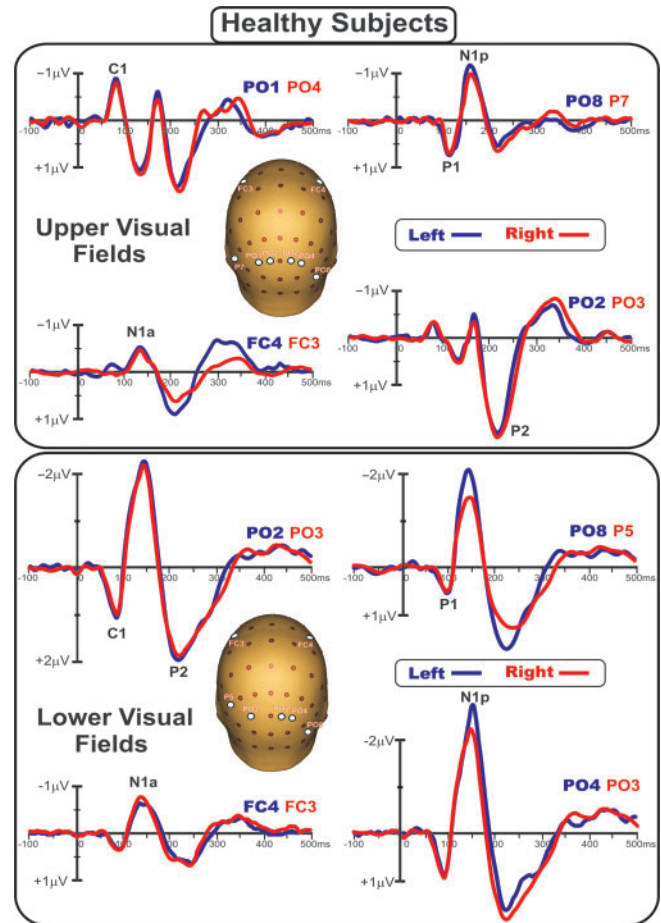


Fig. 4 Healthy subjects. Grand-averaged VEPs. For details see Fig. 2. Waveforms are derived by more than 15,000 trials per quadrant.

and 100 ms for the lower fields. P1 characteristics were very close to those reported for the neglect group.

In both healthy subjects and LBD patients the two sub-components of N1 were well detectable. N1a was prominent at contralateral frontal-central sites and peaked at 135–145 ms, and N1p was distributed over contralateral parieto-occipital sites and peaked at 145–155 ms. In agreement with previous studies (e.g. Di Russo *et al.*, 2002b), the anterior N1a did not change appreciably in latency or amplitude for stimuli at the four spatial positions, while N1p to lower field stimuli was earlier and larger than the N1p to upper field stimuli. Finally, the P2 component peaked at 210–220 ms and was distributed over contralateral parieto-occipital sites.

Voltage topographies

The voltage maps of healthy subjects (see Fig 6), as well as the grand-average recordings, matched perfectly the data recorded in a previous high-resolution localization study combining VEPs and fMRI and which used the same stimulation paradigm (Di Russo *et al.*, 2002b). This match

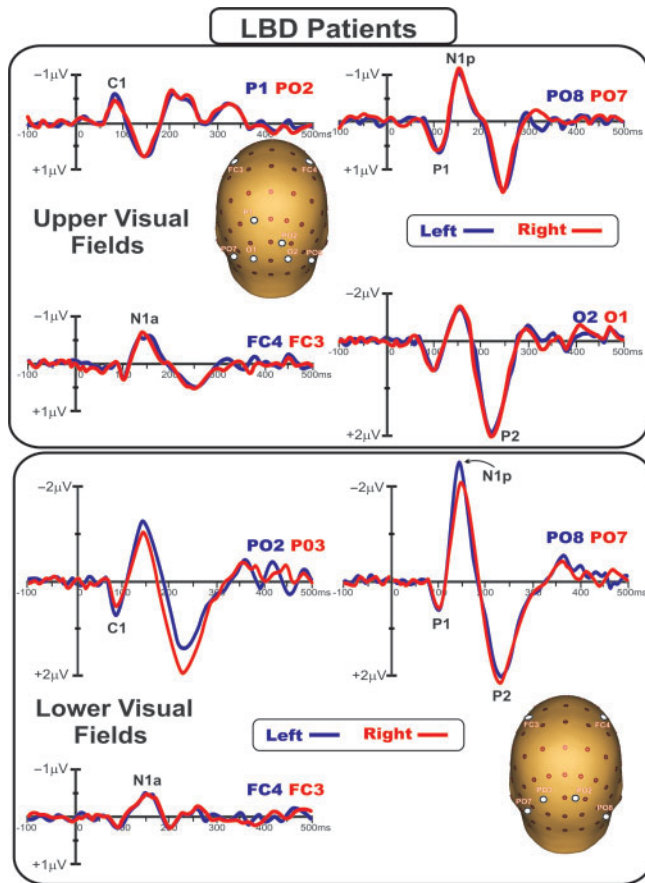


Fig. 5 LBD patients. Grand-averaged VEPs. For details, see Fig. 2. Waveforms are derived by more than 4000 trials per quadrant.

allows us to assume that the neural origin of the VEP components recorded in the present study is the same as that found previously.

Control analyses

As stated in the methods section, all comparisons were planned between left- and right-stimuli responses *within* each group. However, an additional comparison was carried on *between* patients groups limited to the early components’ (C1 and P1) amplitudes and latencies to the four quadrant stimuli to exclude the presence of specific visual sensitivity deficits in neglects. No significant difference was found between groups either for responses to the same quadrants or for responses to contralateral quadrants (all $t_{(15)} > 1.2$ ns).

Discussion

In the study of neglect (and extinction), an open question is whether the visual processing of contralateral stimuli is normal or not; if it is not, the level of processing failure has to be assessed. In the last decade, this question has received little attention; studies have been primarily based on electrophysiological, and rarely on fMRI, recording. The lack of data is not surprising considering the difficulty of applying these techniques in patients suffering from severe brain damage.

The present study contributes to answering this question by analysing the electrical activity of different cortical areas involved in the processing of left and right visual field stimuli. Results showed two main functional impairments

Table 3 VEP components identified in healthy subjects

VEP component	Stimulus position	Peak electrode	Peak latency	P-value	Peak amplitude	P-value
C1 (70–90 ms)	Upper left	PO1	80	ns	-0.86	ns
	Upper right	PO4	80		-0.83	
	Lower Left	PO2	84	ns	1.13	ns
	Lower Right	PO3	84		0.99	
P1 (90–120 ms)	Upper left	PO8	105	ns	0.75	ns
	Upper right	P7	105		0.72	
	Lower Left	PO8	100	ns	0.65	ns
	Lower Right	P5	100		0.62	
N1a (130–160 ms)	Upper left	FC4	135	ns	-0.67	ns
	Upper right	FC3	135		-0.58	
	Lower Left	FC4	135	ns	-0.55	ns
	Lower Right	FC3	135		-0.68	
N1p (140–200 ms)	Upper left	PO8	155	ns	-1.28	ns
	Upper right	P7	155		-0.95	
	Lower Left	PO4	148	ns	-2.78	ns
	Lower Right	PO3	148		-2.18	
P2 (200–280 ms)	Upper left	PO2	210	ns	2.12	ns
	Upper right	PO3	210		2.16	
	Lower Left	PO2	215	ns	1.98	ns
	Lower Right	PO1	215		1.85	

Latencies (ms) and amplitudes (µV) are measured on the corresponding peak electrode within the indicated interval. P-values indicated the statistical comparison between left and right visual fields. ns = not-significant.

Table 4 VEP components identified in LBD patients

VEP component	Stimulus position	Peak electrode	Peak latency	P-value	Peak amplitude	P-value
C1 (70–90 ms)	Upper left	PO3	84	ns	−0.46	ns
	Upper right	PO2	84		−0.61	
	Lower Left	PO2	84	ns	0.73	ns
	Lower Right	PO3	86		0.65	
P1 (90–120 ms)	Upper left	PO8	110	ns	0.82	ns
	Upper right	PO7	105		0.77	
	Lower Left	PO8	100	ns	0.62	ns
	Lower Right	PO7	100		0.59	
N1a (130–160 ms)	Upper left	FC4	140	ns	−0.64	ns
	Upper right	FC3	140		−0.69	
	Lower Left	FC4	146	ns	−0.44	ns
	Lower Right	FC1	148		−0.47	
N1p (140–200 ms)	Upper left	PO8	150	ns	−1.13	ns
	Upper right	PO7	150		−1.22	
	Lower Left	PO8	144	ns	−2.52	ns
	Lower Right	PO7	148		−2.16	
P2 (200–280 ms)	Upper left	O2	220	ns	1.98	ns
	Upper right	O1	215		2.05	
	Lower Left	PO8	220	ns	2.01	ns
	Lower Right	PO7	216		2.12	

Latencies (ms) and amplitudes (μV) are measured on the corresponding peak electrode within the indicated interval. P-values indicated the statistical comparison between left and right visual fields. ns = not-significant.

specific for left-field stimuli. The first takes place in bottom-up processing at the level of the anatomically intact dorsal parietal areas; the second is located at the level of the reactivation of the striate and extrastriate areas via feedback connections from higher visual areas.

Bottom-up processing of visual stimuli located in the neglected hemifield was spared up to ca. 130 ms from stimulus onset. V1 activity evoked by contralesional stimuli (shown by the C1 component) was comparable to the activity evoked by ipsilesional stimuli. The latency was normal and the polarity inversion for upper and lower hemifields was regularly present. Similarly, the two extrastriate areas (dorsal V3A and ventral V4) responsible for the P1 component generation were activated comparably by left and right stimuli.

Compared to healthy subjects, C1 amplitudes of neglect patients look reduced. However, this does not support the view of any specific contralesional sensory impairment. The amplitude reduction was identical for stimuli displayed in left and right visual field; moreover, C1 amplitude was comparable in patients with neglect and in patients without neglect (LBD patients). The more likely explanation for amplitude reduction is a decrement in the signal-to-noise ratio for high spatial frequency gratings due to aging (both neglect and LBD patients were much older than healthy subjects), possibly associated with unspecific decrement of visual sensitivity (Porciatti *et al.*, 1992). However, effects of drugs cannot be excluded (e.g. Geller *et al.*, 2005).

From studies in healthy subjects (Hillyard *et al.*, 1998; Martinez *et al.*, 2001; Di Russo *et al.*, 2003; Natale *et al.*,

2006), we know that P1 represents the first processing stage at which attentional effects can be documented. According to Natale *et al.* (2006), P1 is modulated by endogenous, sustained focusing of attention. The present data showed that this latter stage of attention-modulated visual processing was normal in the patients with neglect. Consistently, patients with neglect have spared voluntary attentional control (e.g. Natale *et al.*, 2005).

In contrast to the intact early bottom-up striate and extrastriate activity generating the C1 and P1, visual processing in more dorsal areas adjacent to the parietal lobe was profoundly altered. In no patients with neglect we were able to record the N1a component for LVF stimuli, which was expected to be in the 130–160 ms time range. Three studies have localized the source of the N1a in the most dorsal IPS regions, i.e. between the posterior IPS (pIPS) and the horizontal IPS (hIPS) (Martinez *et al.*, 2001; Di Russo *et al.*, 2002b; 2005). These parietal regions are more dorsal than those anatomically damaged in neglect (Corbetta *et al.*, 2005; Committeri *et al.*, 2007); indeed, our MRI data do not indicate lesions in these areas (Table 1). In any case, the absence of N1a for contralesional stimuli was a feature of *all* neglect patients.

This feature cannot be due to an early sensory deficit. Previous works in healthy subjects and patients (e.g. Brusa *et al.* 2001) found that the visual sensitivity is strictly related to the C1 and P1 amplitude and latency, so that lower sensitivity is correlated to smaller amplitude and longer latency of these two early VEP components. In patients with neglect, C1 and P1 to contralesional stimuli

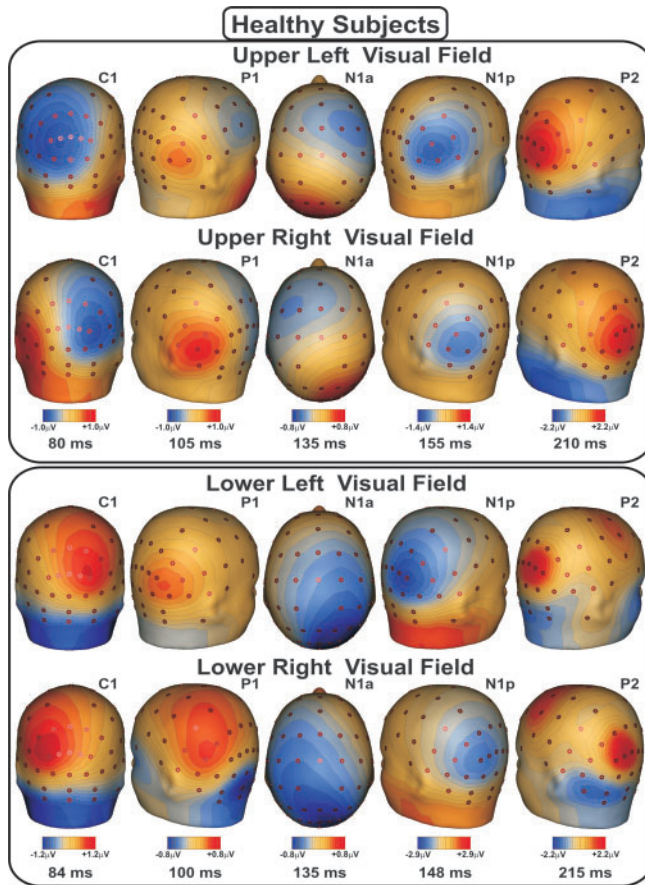


Fig. 6 Healthy subjects. Spline-interpolated 3D voltage maps of VEP components. Note that the N1a topography appears more posterior for lower quadrant stimuli likely because the N1p component reaches the peak earlier, shifting the N1a topography posteriorly.

were found to be comparable to C1 and P1 to ipsilesional stimuli, while N1a was missing only for contralesional stimuli. Moreover, note that in LBD control patients, the N1a contralesional component was comparable in amplitude and latency to the ipsilesional component, despite extended brain lesions (Table 1). Overall, the missing N1a in the neglect patients seems to reflect a functional deficit at a relatively high level of bottom-up stimulus processing rather than structural damage to the neural generators. This view is compatible with Corbetta & co-workers' model of neglect (Corbetta *et al.*, 2005), which predicts functional impairment of the right hemisphere dorsal attention network even when it is anatomically intact.

According to single-cell data from monkeys (Grefkes and Fink, 2005), dorsal IPS areas are concerned with the integration of multimodal information for constructing a spatial representation of the external world. In monkeys, these areas serve as interfaces between the perceptual and motor systems for controlling arm and eye movements in space. In humans, many fMRI studies show that the IPS is constituted by a mosaic of areas subserving goals similar

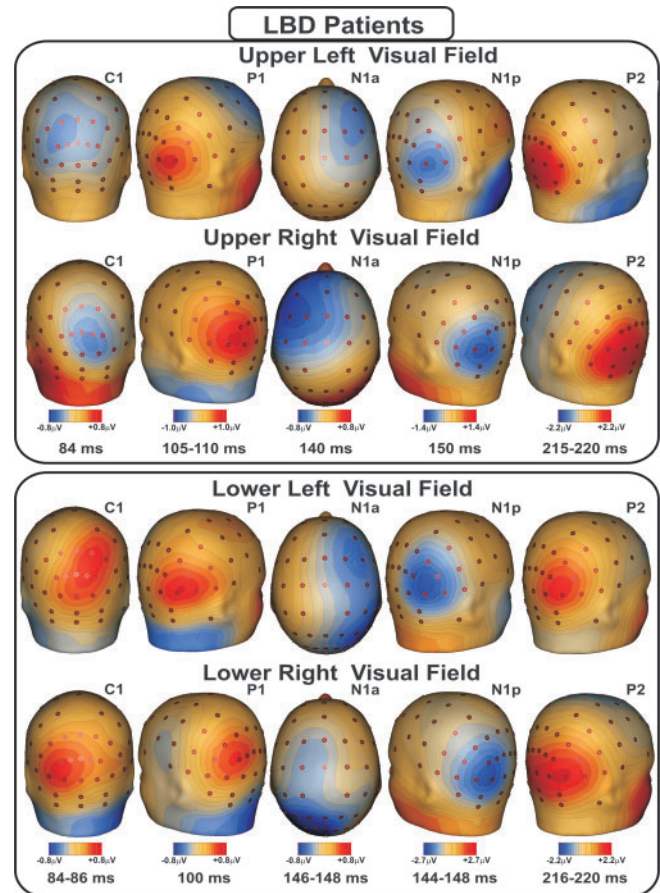


Fig. 7 LBD patients. Spline-interpolated 3D voltage maps of VEP components.

to those described for analogous regions in the monkey. The human dorsal IPS areas deal with spatial attention and visuo-motor control [eye and hand movements (Corbetta *et al.*, 2000; Connolly *et al.*, 2002; Astafiev *et al.*, 2003; Kincade *et al.*, 2005)], contain visuo-topic maps of contralateral space (Serenio *et al.*, 2001; Silver *et al.*, 2005) and are involved in goal-directed stimulus and response selection (Corbetta and Shulman, 2002). A saccade-related area (putative homologue of the macaque LIP) at the confluence of the hIPS and pIPS has been described by fMRI studies (Serenio *et al.*, 2001). The LIP area overlaps with the dorsal IPS region generating the N1a component. Taking all of the data into consideration, we deduce that in humans a processing deficit in dorsal IPS regions may contribute to defective stimulus detection, response and spatial orienting on the contralesional side. This latter behaviour is a typical feature of neglects; note, for example, neglect patients' slow reaction times and modest performance in target detection in the contralesional hemifield, even when uncertainty about stimulus position is excluded (Natale *et al.*, 2005). This deficit was attributed to impairment of the automatic triggering of attention to the site of target presentation following stimulus appearance, which may not be compensated by spared

endogenous attention. The N1a component generated in the dorsal IPS would be the electrophysiological counterpart of this behaviour.

Within a competition model (Marzi *et al.*, 2001), bottom-up signals evoked by ipsilesional stimuli may gain priority for consciousness and action at this neural level, starting about 130 ms from stimulus onset. If defective spatial encoding of an external event and related preparation to act are critical for establishing conscious awareness of the event itself (Berti and Rizzolatti, 1992; Deouell, 2002), we can consider the missing N1a component the electrophysiological counterpart of the defective mechanism for stimulus awareness in neglect.

Another, not alternative, mechanism may be based on top-down feedbacks. As described in the introduction, it seems that the components following the N1a reflect reactivation of visual areas (Nobre *et al.*, 1998; Martinez *et al.*, 2001; Olson *et al.*, 2001; Noesselt *et al.*, 2002; Di Russo *et al.*, 2003). A first feedback stage is represented by the parietal-occipital N1p component (140–180 ms) and a later stage by the P2 component (180–220 ms). These contralesional components were selectively changed in neglect patients (no contralesional change was observed in LBD patients). The latencies of N1p and P2 to contralesional stimuli were longer and/or the amplitudes were reduced compared to ipsilesional stimuli.

The impairment of the contralesional N1p and P2 observed in all patients with neglect supports the hypothesis of defective top-down modulation of visual cortices activity. This impaired feedback might contribute to explain the poor perception/awareness of visual stimuli located on the neglected/extinguished side. In fact, it may be noted that the average fixation time (~ 300 ms) is much longer than the short time used for the transient presentation (66 ms) in the laboratory set. Thus, the time span of a single fixation in ecological conditions is long enough to allow full expression of top-down feedbacks to striate and extrastriate areas. In contrast the effect of this feedback cannot be recorded in the early transient components (C1 and P1). In this view, we suggest that the sensory analysis of the contralesional stimulus taking place in early visual areas after their first activation is not normal.

Let us clarify this suggestion that seems to contradict our previous statement that bottom-up processing is intact up to 130 ms from stimulus onset and V1, V3 and V4 activities are normal. The first activity elicited in V1, V3 and V4 by contralesional stimulus (C1 peaking at 80 ms, and P1 peaking at 100 ms) is intact, but the reactivation of the same areas (as represented by N1p and P2 peaking at 150 and 210 ms) related to the processing of the same stimulus is changed from normal.

As pointed out in the introduction, the role of descending feedback pathways in perception is only partly clear. Evidence for feedback modulation of activity in lower-tier visual areas has been shown in macaque V1 during figure-ground segregation (Kapadia *et al.*, 1995;

Lamme, 1995; Zipser *et al.*, 1996; Hupé *et al.*, 1998; Lamme *et al.*, 1998, 1999; Lamme and Spekreijse, 2000) and motion perception (Sillito *et al.*, 2006). Consistent with reentrant feedback modulations from higher-tier areas (Lamme and Roelfsema, 2000), these modulations occurred considerably later than the initial onset of activity of the same V1 neurons (Zipser *et al.*, 1996; Lamme and Spekreijse, 2000) and were suppressed by anesthesia in higher areas (Lamme *et al.*, 1998). ERP studies describing the feedback (Nobre *et al.*, 1998; Olson *et al.*, 2001; Martinez *et al.*, 2001; Noesselt *et al.*, 2002; Di Russo *et al.*, 2003) proposed that it might improve the salience of stimuli to attended locations. Indeed, at the single-cell level feedback pathways facilitate the basic visual processing responsible for figure-ground segregation and motion direction perception. Defective feedback, such as in patients with neglect, may impair stimulus perception of both stationary and moving stimuli. Previous studies suggested that the source of feedback to V1 might be the posterior fusiform gyrus (area V4/V8) and the source of feedback to extrastriate areas might arise from areas in the inferior temporal cortex, considered the human homologues of macaque areas TEO and TE (e.g. Olson *et al.*, 2001).

In the present study with transient stimulation, we were able to detect V1 reactivation (P2 component). However, reactivation was certainly dominant together to V5/MT activity in the SSVEP condition. V1 and MT/V5 are in fact the main generators of SSVEP (Di Russo *et al.*, 2007), and the SSVEP averaging time is on the order of many seconds, thus, allowing full expression of defective top-down feedback on V1. Consistent with the idea that SSVEPs allow full expression of top-down feedbacks, we observed in neglect patients changes of the SSVEP to LVF (neglected) stimuli with respect to RVF stimuli (see supplementary Table 1). Also, in healthy subjects, changes of SSVEP analogous to those recorded in neglect were associated to attended vs. unattended stimuli and good vs. poor awareness of the stimuli (see supplementary Table 2); (Di Russo and Spinelli, 2002a).

In summary, the present data obtained with transient VEP in neglect patients allowed for the localization of the contralesional input processing deficit in time and space. Bottom-up processing around 130 ms at the IPS level is defective, and top-down feedback in striate and extrastriate areas in the range 140–220 ms is impaired. The correlate of such defective electrophysiological signals is a visuo-motor and perceptual deficit, with poor awareness, slow reaction times and poor detection of stimuli in the contralesional hemifield.

The present data contribute toward an understanding of neglect syndrome and may offer electrophysiological markers for measuring recovery.

Supplementary material

Supplementary material is available at *Brain* online.

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